Topical Immunotherapy in Alopecia Areata

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According to present knowledge, topical immunotherapy is the most effective approach to induce hair regrowth in patients with alopecia areata [1]. The patient is sensitized by application onto the scalp of a potent contact allergen, and subsequently a mild allergic contact dermatitis is elicited by weekly applications of the same contact allergen. It should be noted that the effectiveness of this treatment has not been proved by double-blind randomized crossover studies. Such studies are unfeasible but fortunately unnecessary. Whether a topical treatment is effective or not in alopecia areata is convincingly shown by unilateral treatment (Fig 1). This approach has provided evidence that topical immunotherapy combines a high success rate with a low incidence of side effects [2].

The spectrum of side effects, the issue of toxicologic safety as well as practical guidelines regarding topical immunotherapy of alopecia areata, has been reviewed elsewhere [1,3].

Many questions regarding this treatment, however, are still unanswered. The main practical problem is the lack of complete toxicologic data of diphencyprone as obtained from animal studies. As long as these data are incomplete, the drug cannot be recommended for routine treatment. The same is true for an alternative contact allergen, squaric acid dibutylester [1].

How does this treatment work? The fact that similar results can be obtained with contact allergens of fundamentally different structures clearly indicates that the therapeutic effect is not due to a specific pharmacologic mechanism but to the immune response common to all of these allergens [3]. Topical immunotherapy can therefore be used as a model for the immunologic elucidation of alopecia areata. We have compared the immunohistochemical findings in tissue samples obtained before and during treatment, or obtained simultaneously from either side in a patient receiving unilateral treatment. In this way we have shown that in untreated alopecia areata the peribulbar infiltrate consists predominantly of CD4 + T cells with a CD4:CD8 ratio of approximately 4:1, whereas during successful treatment with diphencyprone the mean CD4:CD8 was 1:1, and in patients with poor or no response to treatment the ratio was 0.7:1 [4]. This was an initial step to provide evidence that the therapeutic effect may be ascribed to topical immunomodulation.

Normal anagen hair bulbs do not express detectable amounts of class I and class II major histocompatibility antigens. By contrast, biopsies from untreated alopecia areata show expression of these antigens on hair matrix epithelium and, to a lesser degree, on the subinfundibular epithelium. In biopsies obtained from areas that had received topical immunotherapy, this abnormal expression of HLA-A,B,C and DR antigens in the epithelium of hair bulbs was shown to disappear in part or even completely [5].

In hair bulbs of healthy individuals, Langerhans cells are only rarely seen. Untreated alopecia areata is characterized by an abnormal intrabulbar and peribulbar accumulation of $CD1^+$ dendritic cells [1]. Under topical immunotherapy, the intrabulbar Langerhans cells tend to disappear [5]

When these findings are taken together, the essential mechanism inducing hair regrowth under topical immunotherapy is far from clear. An attractive explanation, however, would be antigenic competition resulting in topical immunomodulation. The peribulbar T-cell infiltrate observed in untreated alopecia areata would reflect a cell-mediated immune reaction to a hair-associated antigen. Topical immunotherapy would introduce a second antigen at the same site. The repeated application of diphencyprone would give rise to local accumulation of both helper and suppressor T cells. The suppressor

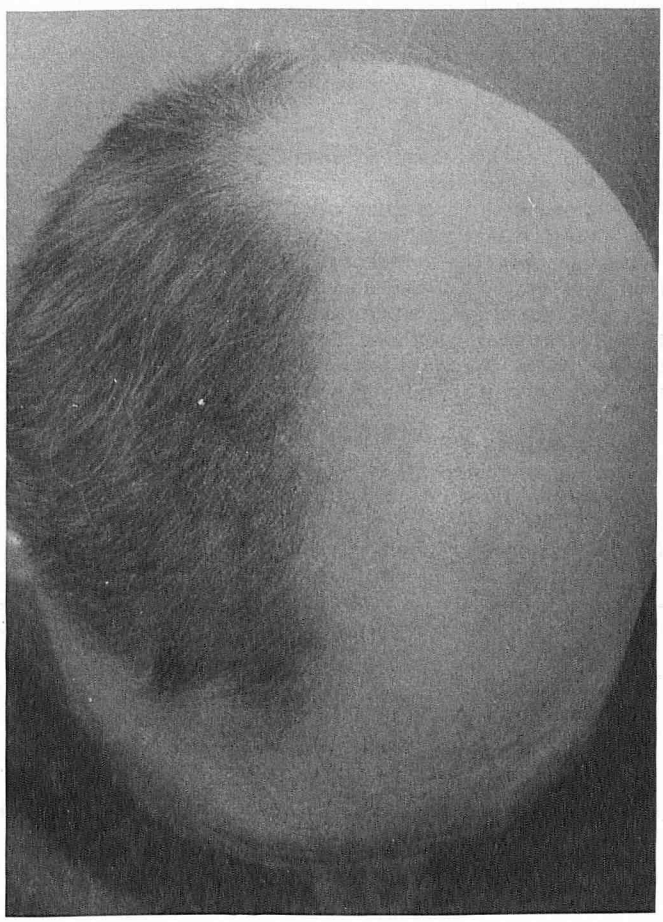

Figure 1. Unilateral hair regrowth induced in alopecia totalis after 18-week unilateral treatment with diphencyprone.

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T cells would exert, by means of soluble mediators, both specific and non-specific inhibitory effects in order to assure a negative immunoregulation. In other words, a "switch-off mechanism" inherent in the therapeutically induced allergic contact dermatitis would non-specifically inhibit the immune reaction to the as yet unknown hair-associated antigen that is assumed to form the main target in the pathogenesis of alopecia areata [6]. To discover and analyze this antigen, or group of antigens, appears to be a major task in future research on alopecia areata.

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Isoprinosine Treatment of Alopecia Areata

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Isoprinosine (inosine pranobex) is composed of inosine and the p-acetamidobenzoic acid salt of N,N-dimethylamino-2-propanol in a 1:3 molar ratio. The rationale underlying the use of the drug to treat disorders of immune function is the hypothesis that lymphocytes may produce an inosine-containing essential substance not synthesized by other cell types. (Transfer factor, for example, contains inosine.) Isoprinosine has been reported to exert antiviral and antitumor effects in vivo that are secondary to its capacity to potentiate the differentiation, proliferation, and function of lymphocytes [1].

PHARMACOLOGY

Early data demonstrated that the antiviral effect of isoprinosine in vivo depended on some factor or factors present in the intact host but not in tissue culture systems used for in vitro antiviral assays. A possible immunopotentiating effect for the drug was suggested by a study that showed that, although it could suppress influenza A_2 infections in mice, this protective effect was eliminated when the animals were simultaneously treated with immunosuppressive doses of either cortisone or antilymphocyte serum. Additional reports have ascribed a variety of immunopotentiating properties to isoprinosine, at least some of which may be secondary to its purported thymic hormone-like activity.

PHARMACOKINETICS

Isoprinosine is rapidly absorbed after oral administration, with peak plasma concentration occuring after 1 h. Plasma half life is extremely short, with drug concentration decreasing to undetectable amounts 2 h after administration. The major excretion product of the inosine moiety is uric acid, which may give rise to transient hyperuricemia. However, attacks of gout have not occurred. The p-acetamidobenzoic acid and N,N-dimethylamino-2-propanol components are excreted in the urine as glucoronidated and oxidized products, respectively, as well as being excreted unchanged.

The recommended dosage of isoprinosine in adults is 1 g 4 times a day or, in children, 50 mg/kg/d in divided doses. Neither carcinogenicity, mutagenicity, nor teratogenicity has been associated with the drug.

Table I. Conditions for Which Isoprinosine Treatment Is Reported to Be Beneficial

Herpesvirus infections
Subacute sclerosing panencephalitis
Genital warts
Influenza and rhinovirus infections
Viral hepatitis
Human immunodeficiency virus infection
Autoimmune disorders (including alopecia areata)
Immune suppression associated with aging, burns, cancer, etc.

SPECTRUM OF CLINICAL ACTIVITY

Scattered reports attest to the efficacy of isoprinosine in a variety of viral, neoplastic, and immune-mediated diseases (Table I) [1]. Most studies have been preliminary in nature and suffer from deficiencies in design or in the reporting of their results. Space considerations allow discussion of only two possible uses for isoprinosine: in patients infected with the human immunodeficiency virus (HIV-1) and in patients with alopecia totalis/universalis.

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